ON A GENERAL DEFINITION OF THE SET OF NATIVE CONFORMATIONS FOR GLOBULAR POLYPEPTIDES:

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Abstract:

Here we question the generality of the conventional definition of a native conformation –as the 3-dimensional conformation of an entire globular polypeptide molecule. Although considered common knowledge, and thus not explicitly stated in modern writings, this definition of native conformations has a history as old as the protein folding problem. We attempt a more applicable definition that better correlates with functional activity and thus may be a more suitable substitute for the current convention.

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Introduction:

Historically (and conventionally), the native conformation for a globular peptide has been and still is referred to as the global peptide conformation that is assumed in order for a peptide to perform the function(s) which is/are ascribed to it. Both seminar works by Anfinsen[1], and Mirsky and Pauling[2], define native conformations in terms of entire 3- dimensional conformations assumed by a continuous peptide chain. However, the notion of a special conformation or set of conformations that can be attributed to a global peptide structure may not be generalized for all globular peptide molecules. In other words, function may not always derive from the entirety of the peptide structure, especially when considering large proteins. Thus, efforts founded on a presumed significance of correlations between function and global peptide structure may yield results that are more peripheral to a central underlying theme.

Here we attempt to define structural features of peptides that strongly correlate with their respective functions, and therefore on which basis native peptide conformations can be generalized. We propose that the set of native conformations for a peptide molecule with a single activity is equivalent to the set of conformations occurring at active and allosteric regions during activity. **Active regions** as used here refer to those regions of a peptide that are most-closely associated with the given processes that define the activity of a peptide.

Analysis 1: Polypeptides *without* Allosteric modulation:

To understand the stated proposition, consider the set of procedures that must be in effect during experimental determination of native conformation(s) of a peptide molecule. Note that by stating experimental approach, we are supposing strict reliance on observation of structure and function, as opposed to determination of function by way of comparison to known homologs whose structures and functions have previously been determined. Since the definition of the set of native conformations necessitates a peptide molecule, while assuming or transitioning through such conformations, affect an outcome which is presumed to result from an activity. It should follow that experimental determination of peptide conformation involve procedures that assess these conformations during activity. Another way to put it is that all conformations and conformational transitions that are required for activity must be noted to ***only*** occur with observation of activity.

In addition, if the parameter chosen for definition of activity is occurrence of an outcome (i.e., reaction products in case of enzymatic activities) whose only means of occurring under the experimental condition involve processing by the peptide of interest, then detection of such an outcome under the given experimental condition should indicate activity. Thus, the set of conformations and conformation transitions that ***must*** occur in order to note the stated outcome, can be considered sets of native conformations and native conformation transitions, respectively, of the peptide. Note that this is a non-rigorous schema, but serves as a starting point.

A question that remains to be answered is whether such observations involve analysis of any given region of the peptide, or restricted to the active region. This is an important consideration

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since, in principle, non-active regions may assume conformations that are observed with activity, but do not pose any influences on activity. For instance, consider two peptide regions, one being active and the other non-active. Let us suppose that whereas the active region can assume n_x number of conformations that only occur during activity, the non-active region can assume n_y number of conformations irrespective of occurring activity. If we suppose that in their physiologically folded states conformational changes at any one of these regions has no effect(s) on the other; then it should follow that during activity, conformation transitions about active regions do not affect transitions at non-active regions, and transitions about non-active regions do not affect transitions at active regions, and therefore does not affect activity. If, however, both regions are observed during activity or considered in determination of number of native conformations; then an experimenter may consider the total number of native conformations as a combination of conformations occurring at both regions.

$$\text{Total number of native conformations} = n_x \times n_y$$

However, in actuality only n_x conformations are necessary for activity. Thus, in this sense, the experimenter commits errors in both considerations of less relevant regions in definition of native conformations and estimation of size of set of native conformations. The estimated ensemble will be larger than the actual value. In other words, determination of native conformation(s) from analysis of both regions (regions assuming and transitioning through **activity-determining conformations** (**ADC**s) and those without such conformations) may lead to overestimation of ensemble size. Such estimations can result from global peptide analysis of native conformations.

Analysis 2: Polypeptides ***with*** Allosteric modulation:

For some proteins, activities are regulated via allosteric mechanisms, thereby creating a modulatory system for these activities. Modifications at these allosteric sites (via electrostatic interactions with modulators, covalent bond formation such as with phosporylation by kinases) can alter protein activities. Modulators can be divided into positive and negative factions. Whereas posivitve modulators enhance peptide activity, negative modulators decrease activity. Thus, for the case of allostery, we can consider some conformations at these allosteric regions to be ADCs, even if they may not be active regions per se. Regarding this last point, allosteric sites are not directly involved in the given activity, but instead modulate activity via intereactions between spatially distinct regions on a peptide. However, since there exist a set of conformations at allosteric sites that when transitioned, result in changes in activity at active regions, we consider such a set as members of the set of native conformations of the peptide molecule. Thus, we can define the set of native conformations as the set of conformations occurring at active and allosteric regions of a peptide during activity. That is, regions that can assume ADCs.

Conclusions from stated proposition:

Two conclusions can be drawn from such considerations. The first is that global peptide conformations or conformations at a single or multiple local peptide regions can be considered in association with native conformation(s), if and only if activity derives from such conformations and conformation transitions (CTs). The second is that the peptide can transition between native and

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non-native conformations during activity and non-activity, respectively. Thus, the peptide may not fold into a permanently native conformation as conventionally implied, but **transition-into** and **transition-away** from native conformations. The implications of such conclusions is: for the two state model of protein folding dynamics –An unfolded, non-native conformation and folded native conformation– becomes a three state model consisting of an unfolded, non-native conformation; a folded, non-native conformation (inactive peptide), and a folded, native conformation (active peptide).

References

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